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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCGILLEM, LAURA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,520	BISHOP ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7 and 10-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-7,10-17,20-25 and 28-32* is/are rejected.

7)☒ Claim(s) *18,19,26 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/23/2006 has been entered.

It is noted that claims 8-9 have been cancelled, claim 10 has been amended and claim 32 has been added in the submission filed 8/23/2006. Claims 1-4, 6-7 and 10-32 are under examination.

Claim Rejections - 35 USC § 112

Applicant's arguments, see remarks, filed 8/23/2006, with respect to claims 1-4, 6-7 and 10-31 under 35 U.S.C. 112, first paragraph have been fully considered and are persuasive. The rejection of claims 1-4, 6-7 and 10-31 under 35 U.S.C. 112, first paragraph has been withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is vague and indefinite because it recites the phrase "weak promoter" and the metes and bounds of the weakness of the promoter required are not clear so that the skilled artisan would know whether a particular promoter would meet the limitation of the claims.

Claims 10 and 32 are vague and indefinite because it recites the phrase "modified Rous sarcoma virus (RSV) promoter" and the metes and bounds of how the RSV promoter can be modified and still meet the limitation of the claim are not clear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-7, 12-17, 20-25, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (U.S. Patent No. 5,631,153, view of Sedivy et al. (of record).

Applicants claim a somatic cell gene targeting vector comprising a gene targeting construct comprising a first cloning site operably linked to a DNA encoding a positive selection marker, a second cloning site and a first polyadenylation sequence, wherein the construct is promoterless; and an expression cassette comprising a promoter operably linked to DNA encoding a negative selection marker and a second polyadenylation sequence. The vector further comprises a first- and second- site

specific recombination sequence such as loxP for a recombinase such as Cre recombinase where the recombination sequences flank the DNA encoding the positive selection marker The cloning sites comprise DNA segments that are homologous to genomic target sequences. Applicants also claim a method for disrupting a gene of interest by introducing the claimed vector into a somatic cell so that the first and second genomic target sequences recombine with the gene to yield a genetically altered cell.

This rejection is being maintained for the reasons of record in the previous Office Action, mailed 4/19/2006 and for reasons outlined below.

Applicants submit that the criteria to establish a *prima facia* case of obviousness has not been met such that obviousness cannot be established by combining the teachings of prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination. Applicants cite *In re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995), *In re Laskowski,* 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989), *Grain Processing Corp. v. American Maize-Prods. Co.* 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988), *In re Kahn,* 441 F.3d 977, 986 (Fed. Cir. 2006). Applicants submit that applicant's disclosure cannot be used as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art and an Examiner must not merely cite references showing that the claimed elements or sub-combinations of them were known. Applicants submit that mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole.

Applicants submit that Capecchi et al do not disclose polyadenylation sequences operably linked to the positive selection marker, as recited by claim 1. Applicants submit that Capecchi et al. list a number of "regulatory sequences" that can be used to control expression of the negative and/or positive selection markers and states that the "regulatory sequences" are, e.g., "enhancers and promoters" (col. 13, lines 65-67). Applicants submit the Wikipedia definition of a "regulatory sequence" (also called regulatory region or - element) as "a promoter, enhancer or other segment of DNA where regulatory proteins such as transcription factors bind preferentially. They control gene expression and thus protein expression." (Wikipedia, August 3, 2006). Applicants submit that polyadenylation sequences are not "regulatory sequences" as this term is used by Capecchi et al. Applicants submit that even if Sedivy were to teach the use of a polyadenylation sequence, there is no teaching or suggestion in Capecchi et al to insert a polyadenylation sequence into the gene targeting cassette, because Capecchi et al teach that various "regulatory sequences" can be interchanged, but do not teach that polyadenylation sequences can be added to the gene targeting cassette. Applicants submit that there is no motivation to pick one element (a polyadenylation sequence) out of Sedivy and insert it into the construct of Capecchi et al. Applicants submit that Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector, as recited in claim 1.

Applicants submit that Capecchi et al do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences (as recited by claims 2-4). Sedivy suggests that sequential gene targeting

can be facilitated by recycling a positively selectable gene by using cre-lox system of site-specific recombination (Sedivy at page 90). Applicants submit that Capecchi et al. do not teach or suggest sequential gene targeting, so that one of skill in the art would not have been motivated to modify the construct of Capecchi et al by inserting the cre-lox PNS cassette of Sedivy into their construct.

Applicants submit that even if one were motivated to modify the Capecchi et al construct by inserting the cre/lox PNS cassette of Sedivy, one would have added a positive-negative selection cassette that includes both a promoter-driven neo resistance gene, as well as a thymidine kinase gene, because that is what Sedivy taught. Applicants submit that Sedivy did not teach the combination of a promoterless positive selection marker in combination with a cre/lox system. Applicants submit that Sedivy discloses PNS vectors where the positively and negatively selectable genes are functionally independent expression cassettes, and each contains its own promoter and polyadenylation signals (p. 88, second column and Fig. 1). Applicants submit that Sedivy also discloses promoterless vectors, and PNS vectors, but not promoterless PNS vectors. Applicant asserts that one of skill in the art would not have modified Sedivy to use a promoterless PNS vector, considering Sedivy himself was aware of PNS vectors and promoterless vectors (see Figure 1), and yet did not teach or suggest a promoterless PNS vector. Applicants submit that the motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention, and there is no

motivation in Sedivy to modify the constructs disclosed therein to generate a promoterless PNS vector.

Applicant's arguments filed 8/23/2006 have been fully considered but they are not persuasive.

Although Sedivy et al discloses promoterless vectors, and PNS vectors, but not promoterless PNS vectors, Capecchi et al does teach promoterless PNS vectors. "When, for example a promoterless positive selection marker is used as a third DNA sequence such that its expression is to be placed under control of an endogenous regulatory region..."(see Capecchi et al column 9, lines 10-16, in particular). "The positive selection markers... may be... constructed so that homologous recombination will place it under control of the regulatory sequences in the target sequence" (see column 8, lines 26-34). Therefore, Sedivy et al does not have to teach the combination of promoterless vectors, and PNS vectors, because Capecchi et al teach that information. In addition, Capecchi et al teach the negative selection marker can be diphtheria toxin and exemplify a vector comprising the HSV-TK gene (see column 7, lines 18-20, Table I and column 22, lines 59-67, for example).

Although Capecchi et al do not disclose excision of the positive selection sequences using site-specific recombination sequences, Capecchi et al do teach integration of portions of the PNS vectors into a target cell genome via homologous recombination (see column 5, lines 23-35, for example). While Sedivy et al does not specifically teach the combination of a promoterless positive selection marker in combination with a cre/lox system, Sedivy et al does contemplate use of the cre/lox

system for homologous recombination to introduce a positive selection marker into a genome.

Applicants suggest that the skilled artisan would not be motivated to combine Sedivy et al and Capecchi et al because Sedivy suggests that sequential gene targeting can be facilitated by using cre/lox system, but Capecchi et al do not teach or suggest sequential gene targeting. Applicants further submit that even if one were motivated to modify the Capecchi et al construct by inserting the cre/lox PNS cassette of Sedivy et al, one would have done it to make precisely the vector that Sedivy taught. However, in order to obviate the claimed vector and method of using that vector by combining two references, the skilled artisan does not have to produce the exact combination of the components of the two vectors.

The Cre/lox recombination system is well known in the art. Sedivy et al does contemplate use of the cre/lox system in vectors and methods for gene targeting using a PNS vector. Capecchi et al teach methods of integration of portions of the PNS vectors into a target cell genome via homologous recombination, using vectors with regions homologous to the target sequence. It would have been obvious to use include loxP sequences in a promoterless PNS vector in order to facilitate homologous recombination with a target sequence because the Cre lox recombination system is a well-known and effective method for recombination. It would have been further obvious to introduce a Cre recombinase to the cell after the promoterless PNS vector has been introduced in order to be able to use the loxP sites to remove the positive selection marker because Cre recombinase is functional at the lox P site. The motivation to use a

site-specific recombination system like Cre/lox with a recombinase is the expected benefit of being able to remove the positively selectable marker from the genome if desired. Capecchi et al does not have to teach or contemplate sequential gene targeting for the motivation taught in Sedivy to apply since both references teach vectors using homologous recombination to introduce a positive selection marker into the genome for method of gene targeting.

Applicants submit that there is no teaching or suggestion in Capecchi et al to insert a polyadenylation sequence into the gene targeting cassette. Applicants submit that polyadenylation sequences are not "regulatory sequences" as this term is used by Capecchi et al. Applicants submit that Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector.

Capecchi et al teach multiple regulatory sequences for use with the selection markers including SV-40 early and that other known regulatory sequences may be used in controlling the expression of positive or negative selection markers (see column. 13, lines 55-67 and column 14, Table IIB). Applicants submit that the Wikipedia definition of a "regulatory sequence" does not include polyadenylation sequences. However, the content on Wikipedia is collaboratively written by the public, edited at any time and is not officially peer reviewed. In fact, as of the last modification, listed as 8/25/2006, “polyadenylation signals” are included in the definition of regulatory sequence. (Note: Examiner did not make the addition.)

Sedivy et al teach a PNS vector comprising a polyadenylation signal at the 3' end of the positive selection marker and also a polyadenylation signal at the 3' end of the negative selection marker. Sedivy et al also teach a promoterless vector comprising a polyadenylation signal at the 3' end of the positive selection marker (see page 88, Figure 1, in particular). Clearly, Sedivy et al intends a polyadenylation signal at the end of each selectable marker coding region. Polyadenylation signals and polyA tails are well known in the art as important structures for transcription and translation. Capecchi et al do teach that the positive selection marker can in some cases comprise a polyadenylation sequence (see column 13, lines 26-49, in particular) so Capecchi et al contemplate use of polyadenylation sequences. Since Capecchi et al teach a promoterless positive selection marker in a PNS vector and methods to target genes with the vector, it would be obvious to include a polyadenylation signal at the end of each marker gene as taught by Sedivy et al, in order to get proper transcription and translation of the markers. It would also be obvious to use an SV40 polyadenylation sequence because Capecchi et al teach that SV-40 early can be used as a regulatory sequence. The motivation to do so is the benefit of being able to produce functional selection markers in order to perform the intended gene disrupting method.

As described above, one would be motivated to add polyadenylation sequence operably linked to both the positive and negative selectable markers to use in somatic cells. It is not necessary to specify a motivation to combine a vector comprising a promoterless positive selection marker with a PNS vector as taught separately by Sedivy et al, since a promoterless PNS vector is taught by Capecchi et al. The

motivation to use this vector in a method to disrupt genes in somatic human cells is the benefit, as taught by Sedivy et al, of being able to study basic questions in cell biology in cultured cells without the complexities of animal models because well defined and easily manipulated experimental systems offer advantages of clonal homogeneity, ability to manipulate external environments, easy transition to biochemical experiments and further, to be able to target human genes in human somatic cells for use in gene knock-out experiments that might be ethically unacceptable in the human germ cell line (see page 88, right column, 1st paragraph, for example).

Capecchi et al teach and claim a method for selecting a transformed cell containing a modification in a target DNA sequence in the genome of the cells after transfection with a targeting vector, selecting against transformed cells containing the negative selection marker and selecting for cells containing the positive selection marker, which reads on identifying the genetically altered cell. Capecchi et al teach and claim that the method can comprise a second modification of the genome of the cell (see column 29, lines 49-67 and column 30, lines 1-17, for example). Sedivy teach that a Cre/lox recombinase system can be used in sequential gene targeting to remove a positive selection marker from the genome.

It would have been obvious to one of ordinary skill in the art to use a Cre recombinase to remove the positive selection marker from the target cell genome and identify those cells in which the recombination has been successful because Sedivy teach that sequential gene targeting can be significantly facilitated by recycling the positive selection gene The motivation to remove the positive selection marker from the

target cell genome and identify those cells is the expected benefit of allowing the PNS vector comprising that same positive selection gene to be used in the same cells (see page 90, left column , 2nd paragraph, for example), because the attribute of positive selection would be removed from the cell instead of attempting to insert the vector in a cell that already contains a positive selection gene.

Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (U.S. Patent No. 5,631,153), in view of Sedivy et al. (of record) further in view of Pfarr et al (DNA, 1986, Vol. 5, No. 2, pages 115-122)

Applicants claim a somatic cell gene targeting vector wherein the expression cassette comprises a BGH polyadenylation sequence.

Capecchi et al teach a vector to modify a target DNA sequence in the genome of a cell capable of homologous recombination comprising a first homologous vector DNA sequence capable of homologous recombination with a first region of a target DNA sequence, a promoterless positive selection marker sequence, a 2nd homologous vector DNA sequence capable of homologous recombination with a second region of the target DNA sequence, and a negative selection marker sequence (See abstract, column 5, lines 5-35, and column 9, lines 10-15, in particular). Capecchi et al teach multiple regulatory sequences for use with the selection markers including SV-40 early and other known regulatory sequences that may be used in controlling the expression of positive or negative selection markers (see column. 13, lines 55-67 and column 14, Table IIB). Capecchi et al teach that the positive selection marker can in some cases

comprise a polyadenylation sequence (see column 13, lines 26-49, in particular) so Capecchi et al contemplate use of polyadenylation sequences. Capecchi et al do not teach that the use of the vector in somatic cells. Capecchi et al do not teach that the polyadenylation sequence is a bovine growth hormone polyadenylation sequence.

Sedivy et al teach targeted homologous gene recombination in somatic cells using PNS vectors and using promoterless vectors (see page 88, left column, paragraph 2, bridging to right column, and Figure 1 for example). Sedivy et al teach a PNS vector comprising a polyadenylation signal at the 3' end of the positive selection marker and also a polyadenylation signal at the 3' end of the negative selection marker. Sedivy et al also teach a promoterless vector comprising a polyadenylation signal at the 3' end of the positive selection marker (see page 88, Figure 1, in particular). Polyadenylation signals and polyA tails are well known in the art as important structures for transcription and translation. Sedivy et al do not teach that the polyadenylation sequence is a bovine growth hormone polyadenylation sequence.

Pfarr et al teach a comparison of various polyadenylation regions on gene expression in mammalian cells using a downstream galactokinase marker gene. Pfarr et al teach that a BGH poly A region results in galactokinase expression three times higher than that of SV40 early or human collagen polyA regions (see abstract, in particular).

It would have been obvious to one of ordinary skill in the art to modify the teaching of Capecchi et al of a vector to target DNA sequences in somatic cells because Capecchi et al use the disclosed vector in cells capable of homologous

recombination and Sedivy et al teach that gene targeting is important in human somatic cells for use in gene knock-out experiments that might be ethically unacceptable in the human germ cell line. The motivation to do so is the expected benefit as suggested by Capecchi et al and Sedivy et al of being able to target and knock-out genes in human cells in culture without the various complications of stem cells.

It would also have been obvious to modify the teaching of Capecchi et al to include polyadenylation sequences in the PNS vector because Capecchi et al teach that different regulatory sequences to modify gene expression can be used and combined (column 13, lines 65-67, in particular) and Sedivy et al teaches that polyadenylation sequences flank the positive and negative selection sequences in PNS vectors.

It would have been obvious to substitute a BGH polyadenylation for an SV-40 early sequences because Pfarr et al teach that a BGH polyadenylation sequence is more produces three fold higher gene expression compared to SV-40 early polyadenylation sequence. The motivation to do insert polyadenylation sequences is the benefit of being able to get proper transcription and translation of the markers and produce functional selection markers in order to perform the intended gene disrupting method. The motivation to use BGH polyadenylation sequence is the expected benefit of high expression of the selectable marker. There is a reasonable expectation of success in using the claimed polyadenylation sequences in the claimed vector to target somatic cells since this has worked previously in the cited references.

Conclusion

Claims 18-19 and 26-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
9/26/2006

DANIEL M. SULLIVAN
PATENT EXAMINER